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Spatial structure of fibrinopeptide B in water solution with DPC micelles by NMR spectroscopy

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ABSTRACT

Fibrinopeptide B (GluFib) is one of the factors of thrombosis. Normal blood protein soluble, fibrinogen (fibrinopeptide A and fibrinopeptide B), is transformed into the insoluble, fibrin, which in the form of filaments adheres to the vessel wall at the site of injury, forming a grid. However, the spatial structure of this peptide has not been established till now. In this article, GluFib peptide is investigated together with dodecylphosphocholine (DPC) micelles which were used for mimicking the environment of peptide in blood vessels. The spatial structure was obtained by applying 1D and 2D $^{1}H-^{1}H$ NMR spectroscopy (TOCSY, NOESY). It was shown that the fibrinopeptide B does not have a secondary structure but we can distinguish the fragment Gly 9 – Arg 14 with a good convergence (the backbone RMSD for the Gly9 – Arg14 is 0.18 ± 0.08 Å).

1. Introduction

Thrombosis is a pathological formation of blood clots in the bloodstream. It is a serious threat to human health and even life. In place of a damaged blood vessel, cells (platelets) are formed. They stick to the defect clumped together and form a primary platelet thrombus. Further, these platelets and damaged tissue start to produce a special substance that triggers a chain of biochemical reactions. As a result, normal blood protein soluble, fibrinogen (fibrinopeptide A and fibrinopeptide B), is transformed into the insoluble fibrin, which in the form of filaments adheres to a vessel wall at the site of injury, forming a grid. On this grid are deposited and even more clumped together red blood cells – erythrocytes, platelets, and later the white blood cells. This forms a denser clot which continues to grow and ultimately firmly "glues" the defect. Thus, thrombosis is a protective reaction of the organism. If nature has not provided this mechanism, a person would be bleeding from the wound of the vessel until such time as his wall is not restored [1]. Many details of the thrombosis mechanisms are still not clear. Particularly, review of scientific literature shows that the structure of the fibrinopeptide B in the membrane or any other lipid surrounding has not been studied at all.

Another feature of the Glu-1-Fibrinopeptide B is that it is often used for tuning and calibration of electrospray ionization and mass spectrometers [2,3].

By far the majority of solution NMR studies on membrane-bound molecules have been carried out using micelles, typically sodium dodecylsulfate (SDS), dodecylphosphocholine (DPC) or dihexanoylphosphatidylcholine (DHPC) due to their availability in deuterated form [4].

DPC and SDS micelles are the most commonly used for structure determination of membrane proteins and peptides. It is important to favor detergents with small aggregation numbers to obtain small, fast-tumbling PDCs and increase the protein signal because of the reduced surfactant proportion. Zwitterionic detergent micelles such as DPC are used to mimic eukaryote membranes while the negatively charged SDS micelles would resemble bacterial membranes [5].

The purpose of this paper is to investigate, by NMR spectroscopy, the spatial structure of a fibrin responsible for thrombus formation (Fibrinopeptide B) near lipid membrane, which is modeled by dodecylphosphocholine (DPC) micelles considering that one of conditions of thrombosis is the interaction of fibrinopeptide B with the surface of platelets. Therefore, DPC micelles were taken as a model membrane [4–6].

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